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Consent Issues in Genetic Research: Views of Research Participants

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Abstract

Background—With the arrival of large-scale population-based genomic research studies, such as the Precision Medicine Initiative (PMI), the question of how to best consent participants is significant, and in an era of patient-centered research, few studies have evaluated participants' preferences about re-consent and broad consent. Using quantitative methods, this study evaluates participants' views regarding the acceptability of re-consent and broad consent in subjects from the Participant Issues Project.

Methods—450 participants were recruited from a cancer genetics registry, including cancer patients, their relatives, and controls. Participants completed a secure online survey.

Results—Most participants endorsed re-consent when investigating an unrelated health condition or sharing their de-identified data with an investigator at a different institution. Notification rather than re-consent was preferred when studying a different gene but the same disease. Over 80% of respondents endorsed re-consent when parents of a child gave the original consent and the child has now reached adulthood. Preferences for some scenarios varied by history of cancer at baseline, gender, stage of cancer, or case versus control group. The large majority of participants preferred the option to select broad consent categories of research.

Conclusion—Understanding research participants' preferences, including their views on the need for re-consent, are critical to the success of the PMI.

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Keywords

Re-consent; broad consent; participants; genetics

INTRODUCTION

Linking large, well-characterized datasets with sizable biobanks and medical records has introduced new challenges into the traditional informed consent model. As population-based genomic studies continue to expand beyond the scope of the original consent, it is necessary to consider how to ethically and practically obtain informed consent from study participants. One current example of this type of research project is the Precision Medicine Initiative (PMI). The goal of the PMI will be to integrate differences in genetics, lifestyle, and environment to maximize individual disease-specific prevention and treatment [1] and to provide the framework for the development of a national cohort of a million or more Americans, in order to learn more about individualized treatment of disease [2]. An undertaking of this magnitude and complexity presents many issues, such as patient privacy, data access, the use of electronic medical records, sharing of data, and consenting.

Re-use of large, existing cohorts and biobanks for additional research creates a challenge for researchers, research participants, and Institutional Review Board (IRB) staff, including the issue of re-consent of existing and previous research participants. Several areas of debate include concerns regarding the circumstances that necessitate obtaining new informed consent for research activities that differ from the original consent, and the use of a broad consent model, usually defined as a generalized consent framework for future research [3]. In this current environment of fast-moving developments in bioinformatics and omic-technologies [4], all stakeholders must work together to expand efforts to advance the PMI goal of individualized prevention and treatment.

Traditionally, informed consent has involved permission to use participant data and samples for a specific use by specific researchers using a single consent form. Recently, the increased use of stored data and/or biospecimens has necessitated the use of either a re-consenting process or development of a more broad initial consent model. Re-consent involves obtaining an additional, new informed consent from participants to use their previously collected data for a new purpose or to share their data with another investigator. Alternatively, the use of a broad or blanket consent informs participants that their data and samples may be used in the future for unknown research [5].

Previous studies have shown that researchers are divided on the circumstances, if any, in which study participants should be re-consented for secondary use of their data. While some feel that re-consent should routinely occur when using data obtained initially for a different research focus [6], others argue that this process is cost-prohibitive, a violation of autonomy and privacy, and will adversely affect study participation [7]. IRB professionals have also been shown to be divided on the circumstances which would require reconsent [8].

Members of our research group recently compared attitudes of genetic researchers and IRB professionals and found that the level of support for re-consent varied between these

stakeholders, depending on the specific scenario under which re-consent would be required. Both genetic researchers and IRB staff were likely to support re-consent if the new study included a new gene or gene variant, an unrelated condition, or a minor reaching majority age. The majority of both groups, however, did not support re-consent to share de-identified data or samples; i.e., did not see this as necessary [9]. In addition, attitudes of genetic researchers and IRB professionals differ on whether a broad consent model is ethical [10–12].

Ironically, while a cornerstone of informed consent includes respecting and promoting participant autonomy [13], there is a lack of literature related to research participant preferences regarding the need to be re-consented for new projects or the use of a broader-type of consent model. Our group recently employed qualitative methods to explore attitudes related to re- consent in a small group of genetic research participants (n=30) and found that overall, the majority favored re-consent because they viewed this process as an opportunity to keep informed regarding the use of their data. In addition, respondents felt a level of ownership of their data and cited re-consent as a means of keeping control of their information [14]. This current study employs a quantitative survey with a larger set of participants (n=450) to confirm and expand upon the previous work and investigate the views of research participants from the Participant Issues Project (PIP) regarding re-consent and broad consent in genetic research.

MATERIALS AND METHODS

Parent Study

The Northwest Cancer Genetics Network (NWCGN), established in 1998, was among the eight original sites funded by the National Cancer Institute to form the Cancer Genetics Network, a nationwide network of centers to specialize in the study of inherited predisposition to cancer [15]. The Northwest Cancer Genetics Registry (NWCGR), established in 2010, is a continuation of the NWCGN and is the source of data for this project. Cases were recruited via population-based cancer registries and direct referral from health care providers throughout Western Washington (n=2027). Relatives of cases were also recruited (n=451), including family members with and without cancer at baseline. A population-based comparison sample, referred to as “controls,” (n=527) was identified through two sources: 1) those aged 20–64 years were identified through the Washington State Department of Licensing, and 2) subjects over 64 years of age were selected from files of the Health Care Financing Administration (HCFA). Some controls did report cancer at baseline (n=99), reflecting the underlying population from which the cases were drawn. Finally, some participants self-referred to the registry in response to community awareness efforts and included both people with and without cancer (n=904 total; 340/904 with cancer) and are grouped as cases or controls, respectively. Relatives of self-referrals were also recruited for the study and included in the relative group (n=464). Participants enrolled in the NWCGN completed core data questionnaires at baseline and during subsequent follow-up questionnaires. The questionnaires cover a variety of topics, including personal and family history of cancer and other health conditions, tobacco use, and socio-demographic information [16].

Eligibility and Recruitment for the PIP

All individuals who were enrolled in the NWCGR (n=3352) were the source of participants for PIP, and all subjects who were not confirmed to be deceased as of 2010 were eligible to participate. Letters, including informed consent, were sent by US mail inviting individuals to take the online, confidential survey beginning in late 2013. Up to three invitations were sent to participants at approximately two-week intervals. While family members or the post office confirmed eighteen participants as deceased, vital status was not formally evaluated by this study and the number of additional deceased participants was not known. Online surveys were completed by 450 participants, with 228 from the case group, 155 from the control group, and 67 were relatives.

Survey Methods

Development of the PIP Survey—The purpose of the survey was to document the range and frequency of occurrence of concerns and expectations regarding participating in human research studies, including genomic and family studies. Data from a sample of 31 individuals participating in qualitative interviews described previously as part of PIP [17] were utilized to identify the major content areas and to inform potential response categories for the survey. The survey was then developed using the Tailored Design Method [18] as a general guide.

The resulting instrument had a total of 22 questions, and was divided into six general topic areas: decision to participate in research; relationship between researchers and participants; re-consent and broad consent; return of results; use and security of de-identified data; and family communication of health issues. The types of response categories varied based on the question and included either yes/no/not sure options, Likert-scales (e.g., 5-point scales rating agreement, likelihood or importance of the statement with a sixth “don’t know” or “it depends” option) or categorical responses. We report here the results of the items related to consent, which includes two questions regarding re-consent, with several different scenarios queried, and one question related to broad consent, including 3 alternative scenarios.

Internal and external review of the survey instrument was conducted prior to launch of the web-based survey. All survey questions were pretested among a sample of PIP eligible participants with a convenience sample of independent reviewers from the University of Washington (this included staff, faculty, and students). Cognitive interviews were then conducted with 37 PIP eligible participants and changes were made to improve the clarity of the survey questions [19]. Finally, pilot testing of the final web-based survey was conducted to assess any technical difficulties with the web-based format, access to the resulting data, and to confirm the length of time required to complete the final web-based instrument.

The Catalyst survey software, developed by the University of Washington, was used to develop and implement the web-based survey. The survey was confidential, not anonymous, using a unique identification number for each participant, and participants were free to skip any questions that they did not wish to answer. Each participant was provided an individual URL to access the secure survey instrument. Links to each individual survey and the

participant's NWCGR data were retained to reduce the length of the survey and to allow us to utilize existing demographic and other participant information.

All study procedures were approved by the University of Washington's Human Subjects Division, and also by the University of California, Irvine Institutional Review Board. All participants provided informed consent prior to participation.

Statistical Analysis

Demographics, including the distribution of potential confounders, were evaluated for the total study population, and also separately for cases, controls, and relatives. Responses to all questions were first summarized using frequency distributions. Next, for the reconsent question, "I believe it should be mandatory for the researcher to re-contact the participant and ask for permission again when…" followed by five research scenarios, response categories were collapsed into fewer categories for testing and to facilitate interpretation. For example, the five categories of the Likert scales were collapsed into three, combining the "strongly" and "somewhat" categories (e.g., 'strongly agree' and 'somewhat agree' were combined to create 'agree' and 'strongly disagree' and 'somewhat disagree' were combined to create 'disagree'). Chi-square tests (age, gender and education) and ordinal logistic regression for case, control, or relative status were used to evaluate differences in attitudes regarding re-consent and broad consent. The response categories (dependent variable) were ordered and coded as follows: 1) agree and strongly agree as 1, neutral as 2, disagree and strongly disagree as 3; and, 2) yes, ask permission again as 1, no need to ask, but notify me as 2, and no need to ask or notify as 3. With ordinal logistic regression, several cumulative logits are modeled using all possible cut points of the dependent variable, but a single summary odds ratio (OR) and 95% confidence interval describing the relationship between the dependent and independent variable is obtained. Comparisons were adjusted for age, gender and education. R version 3.2.2 was used for all analyses; the polr function from the MASS package was used for ordinal logistic regression) [20]. A p-value ≤ 0.05 was considered statistically significant for all tests. Sample sizes varied by question since participants were allowed to skip any question they did not wish to answer.

RESULTS

PIP survey participant demographics are shown in Table 1. The participant response rate was 13.5% (450/ 3334 (3352-18)). About half of the 450 research participants were cases (n=228), one-third were controls (n=155), and the remainder were relatives (n=67). Overall, the average age was 63.6 years, and the majority of participants were white (94.7%) and well educated, with over 60% having a college degree. Among those participants with cancer at initial enrollment into the parent study (baseline), melanoma was the most frequent cancer type (29.5%), followed by thyroid cancer (18.3%), and breast cancer (15.5%). Thirty-five research participants without cancer at enrollment into parent study reported a cancer at the time of this survey (follow-up).

As shown in Figure 1, when questioned if the participant would like to be asked permission to use their previously collected health information and a sample for a purpose other than what they were initially consented for, only a nontrivial minority (13%–26%) reported they

did not feel the need to be asked permission or notified. Respondents were evenly divided between the need for re-consent versus only informing them when their data will be used for a different, but related condition. The majority of participants preferred re-consent when investigating an unrelated health condition or sharing their de-identified data or sample with a researcher at a different institution. When studying a different gene but the same type of cancer, almost half the participants felt they did not need to be re-consented, but they preferred to be notified. Examination of these same four scenarios by participant type (cases, controls, relatives), gender, and history and stage of cancer at baseline or follow-up is shown in Table 2. Participants with a history of cancer at baseline were significantly more likely to endorse re-consent to study a related condition ($p < 0.01$), unrelated condition ($p < 0.04$), or new gene compared to participants without a history of cancer at baseline ($p < 0.01$). Cases were significantly more likely to favor re-consent for unrelated health conditions and a new gene compared to controls ($p < 0.05$; 0.01, respectively), while stage of cancer was directly and significantly associated with the need for re-consent to study a new gene ($p < 0.05$) or sharing de-identified data with a researcher at a different institution ($p < 0.03$).

The majority of PIP participants agreed that re-contact should be mandatory for all five scenarios (Figure 2) and no differences were seen by participant type (Table 3). While male participants were significantly more likely to endorse re-consent when a minor reaches majority age ($p=0.04$), participants with a history of cancer at baseline were more likely to strongly agree or agree with the need for re-contact to study a different, but related condition ($p=0.01$). These participants were also more likely to strongly agree or agree with the need for re-contact to study an unrelated health condition, or a new genetic factor, but these associations were not statistically significant. The opposite was seen in relation to stage of cancer at follow-up. Participants with a higher stage of cancer at follow-up were significantly more likely to not endorse re-consent. Participant preferences regarding a broad consent model that covers all potential future diseases or genes are shown in Figure 3. The option to select broad consent categories of research was most accepted, with 81%, 75%, and 89% of cases, controls, and relatives, respectively, agreeing or strongly agreeing to this type of research consent.

DISCUSSION

The new era of Precision Medicine will include integration of large genomic databases and samples and electronic medical records, and has resulted in the rekindling of the debate about the need and merits of re-consent. One category of the newly released PMI Privacy and Trust Principles is “Respecting Participant Preferences,” which includes adhering to participant preferences regarding information sharing and re-consent for research [21]. This paper addressed the attitudes of a group of genetic research participants regarding the need for re-consent and broad research consent.

We found that most participants preferred to be re-consented when the new study focused on an unrelated health condition or when sharing de-identified data or samples with researchers at a different institution. Participants also felt that notification alone was sufficient when the new research involved a different gene but the same type of cancer. To our knowledge, only one previous study, limited to the submission of data to the federal database of Genotypes

and Phenotypes (dbGaP), revealed participant preferences regarding consent [22]. Consistent with our findings, 69% of participants felt re-consent was important prior to including previously collected data in a federal database.

In contrast to these findings, previous research has shown that other stakeholders felt differently about consent issues than research participants. Genetic researchers were less likely to favor re-consent when studying a different, but related disease, or when a minor reaches a majority age [23]. It is possible that differences between researchers and participants' choice to endorse re-consent in some scenarios may stem from fear that the re-consent process will hinder participation, be cost-prohibitive, or create insurmountable logistical barriers [7, 23]. It is also possible, and perhaps likely, that researchers lack an understanding of participant preferences. Similar to genetic researchers, IRB professionals are also less likely than research participants to agree with the need for re-consent when sharing samples or data with an investigator at a different institution. However, compared to participants, IRB professionals have been shown to more strongly endorse re-consent when an unrelated cancer or condition or a new genetic factor will be studied [8].

Medical ethicists are divided on whether use of a broad consent is appropriate [24, 25] or unethical [10–12]. In this study, the large majority of research participants supported the use of a broad consent, however over 80% of participants preferred the option to select the broad categories. While some [26, 27] but not all [28] previous studies have supported the use of a broad consent, this is the first study to query research participants rather than survey the general population.

This study population was limited to an educated and mostly white group of adults and application of these results beyond this demographic is not possible. In addition, the source of this population was a cancer registry and their relatives, and it is possible that these results are not representative of a non-research or more diverse population. While this study found no significant differences between preferences of cases, relatives, or controls, 35 participants in the control group reported cancer at baseline and 35 participants without cancer at baseline reported cancer at the time of the survey. While differences in re-consent preferences by stage of cancer were seen, these findings were based on small numbers and further conclusions are not possible. Finally, invitations to participate in this study were sent to 3352 NWCGR participants with 450 participants completing the survey. Although the response rate appears low (13.5%), this is probably a conservative estimate as it not known how many participants died between 2010 and the time of this survey in late, 2013. A comparison by demographics showed that compared to non-responders, responders were slightly younger, more likely to be female, and more educated compared to non-responders. Response rates did not differ significantly between cases, controls, and relatives.

Respect for autonomy is the guiding principle of informed consent in human research. Participants are at the center of the PMI and their preferences are paramount to its recruitment, retention, and overall success. This study illustrates participant preferences regarding re-consent, and these preferences differ from re-consent attitudes of researchers and IRB professionals. It is critical for researchers and IRB's to understand and acknowledge the desires of participants. Likewise, it is important that participants

understand the perspectives and boundaries of researchers, such as cost restrictions and practical limitations of research studies. As population-based genomic research continues to expand, it will be necessary to close this gap between stakeholders to maximize study success. Additional studies are necessary to further understand the participants' perspectives on strategies to overcome barriers to re-consent, and to develop approaches to reach agreement between the stakeholders regarding re-consent and broad consent.

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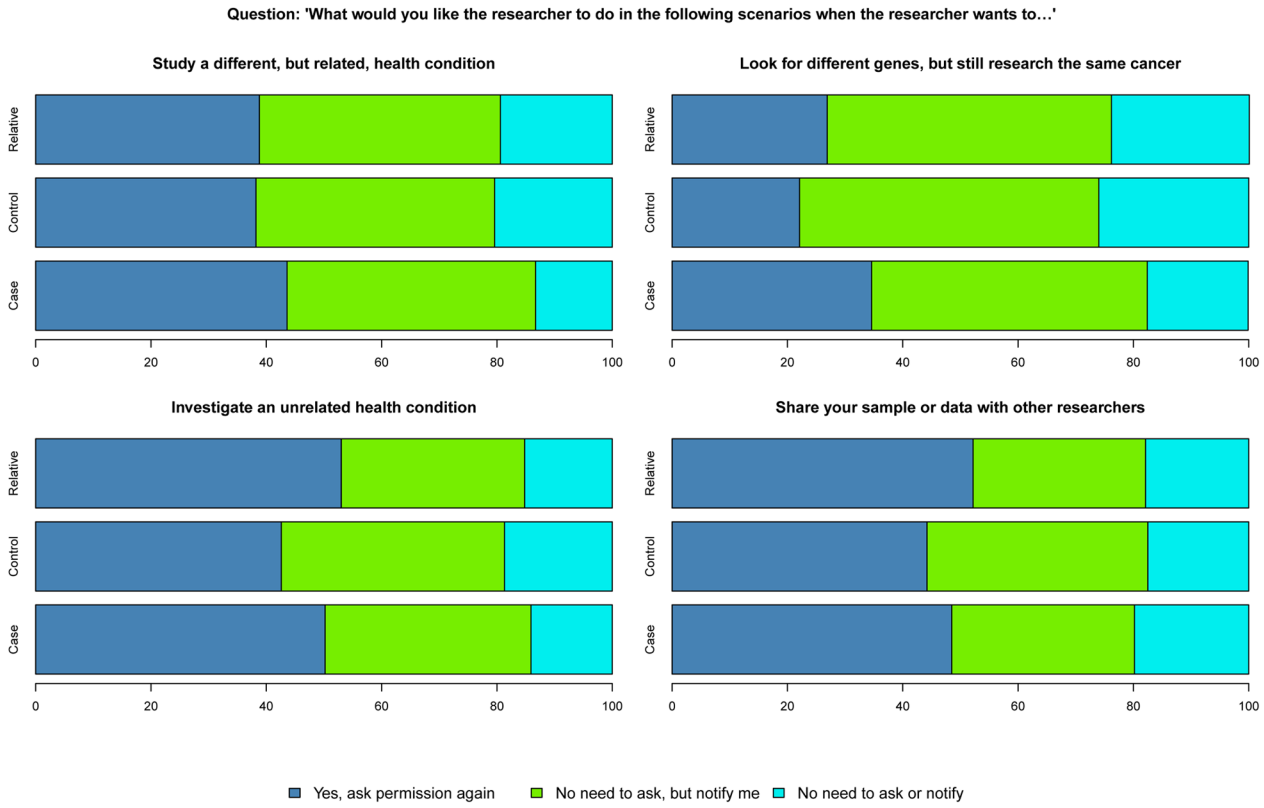

Figure 1.
Patient preference rates regarding re–consent by research scenario and participant type

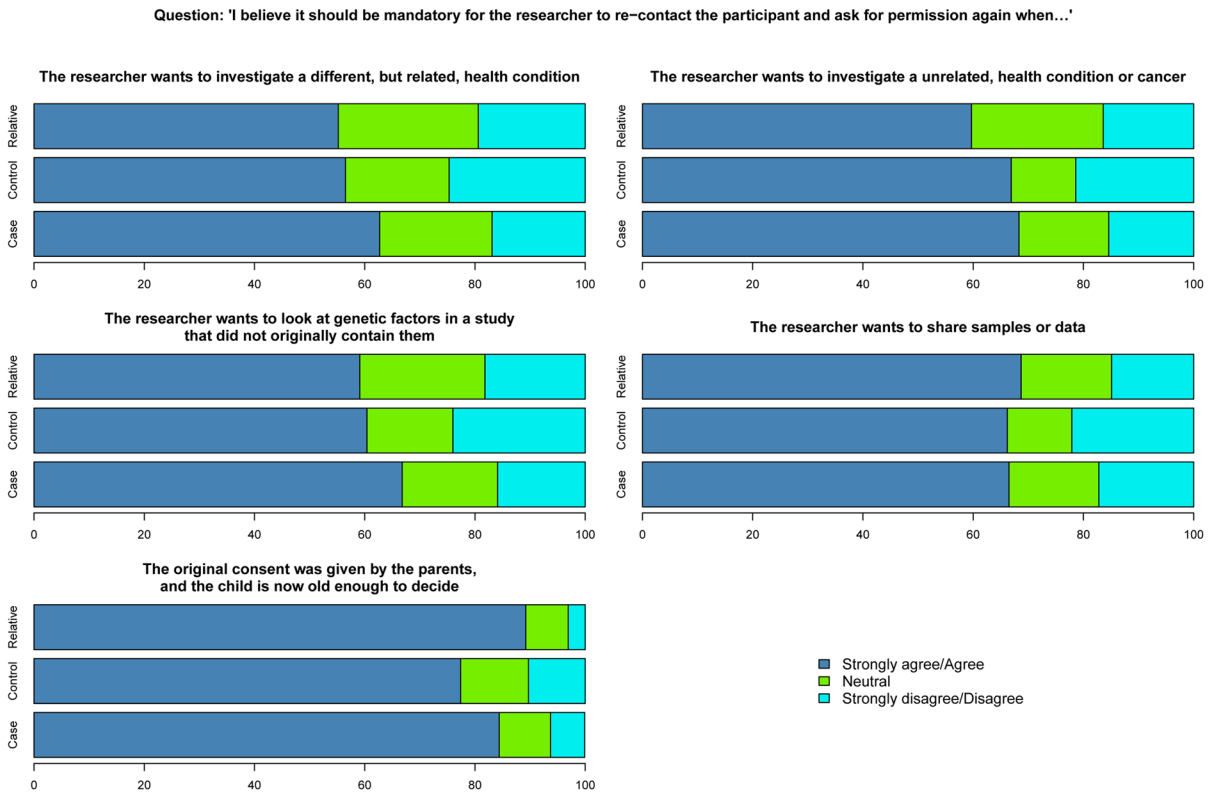

Figure 2.

Patient preference rates regarding re–consent by research scenario and participant type

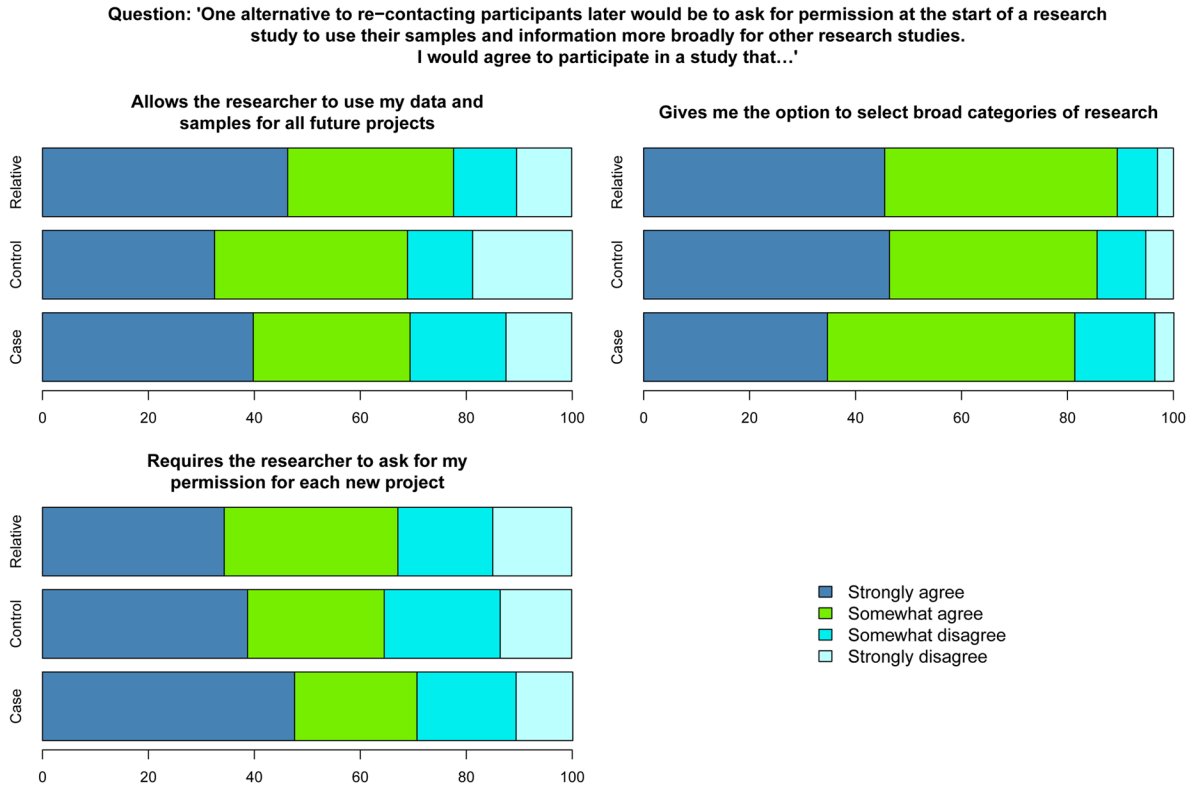

Figure 3.
Patient preference rates regarding broad consent by participant type

TABLE 1

Demographics of the research participant (PIP) group

	Total (N=450)	Cases (N=228)	Controls (N=155)	Relatives (N=67)
Age (yrs) (Mean (SD))	63.6 (11.8)	64.3 (11.4)	64.0 (11.5)	60.5 (13.6)
Women (N (%))	292 (64.9%)	145 (63.6%)	110 (71.0%)	37 (55.2%)
Race (N (%))				
Asian/Pacific Islander	7 (15.6%)	4 (1.8%)	2 (1.3%)	1 (1.5%)
Black	4 (0.9%)	2 (0.9%)	2 (1.3%)	0
Multi-Racial/Other	16 (3.6%)	8 (3.5%)	4 (2.6%)	4 (6.0%)
White	423 (94.7%)	214 (93.9%)	147 (94.8%)	62 (92.5%)
Education (N (%))				
High School or less	40 (8.9%)	19 (8.3%)	13 (8.4%)	8 (11.9)
Some College	107 (23.8%)	57 (25.0%)	37 (23.9%)	13 (19.4%)
Bachelors Degree	276 (61.3%)	126 (55.3%)	105 (67.7%)	45 (67.2%)
Unknown	27 (6.0%)	26 (11.4%)	0	1 (1.5%)

TABLE 2

Adjusted ordinal regression analyses (OR=odds ratio; CI – Confidence Interval) by participant characteristics

Scenario	Model	OR	95% CI	p-value
	Subject Type			
Study a different, but related health condition	Control vs Case	1.45	0.97, 2.17	0.07
	Relative vs Case	1.34	0.78, 2.31	0.29
	Gender	1.19	0.80, 1.76	0.40
	Cancer at baseline	**0.61**	**0.42, 0.88**	**0.01**
	Cancer at follow-up	0.72	0.50, 1.06	0.09
	Stage of cancer at follow-up	2.0	0.76, 5.26	0.16
Look for genes other than the one mentioned in the original consent, but still research the same type of cancer	Subject Type			
	Control vs Case	**1.94**	**1.29, 2.92**	**0.01**
	Relative vs Case	1.51	0.87, 2.62	0.15
	Gender	1.11	0.75, 1.66	0.60
	Cancer at baseline	**0.55**	**0.38, 0.80**	**0.01**
	Cancer at follow-up	**0.67**	**0.46, 0.98**	**0.04**
	Stage of cancer at follow-up	**2.64**	**1.00, 6.92**	**0.05**
Investigate an unrelated health condition, such as diabetes or depression	Subject Type			
	Control vs Case	**1.52**	**1.01, 2.28**	**0.05**
	Relative vs Case	1.04	0.59, 1.83	0.88
	Gender	1.33	0.89, 1.97	0.17
	Cancer at baseline	**0.67**	**0.46, 0.98**	**0.04**
	Cancer at follow-up	0.86	0.59, 1.26	0.45
	Stage of Cancer at follow-up	2.24	0.87, 5.77	0.10
Share your sample or data with a researcher at another institution (first removing personal information)	Subject Type			
	Control vs Case	1.16	0.77, 1.73	0.48
	Relative vs Case	0.91	0.52, 1.59	0.75
	Gender	1.3	0.88, 1.93	0.19
	Cancer at baseline	0.88	0.61, 1.28	0.50
	Cancer at follow-up	1.09	0.75, 1.58	0.66
	Stage of cancer at follow-up	**2.94**	**1.10, 7.85**	**0.03**

*statistically significant results ($p \leq 0.05$) indicated in **bold**

**Scoring of dependent variables as follows: 1) agree and strongly agree as 1, neutral as 2, disagree and strongly disagree as 3; and, 2) yes, ask permission again as 1, no need to ask, but notify me as 2, and no need to ask or notify as 3

TABLE 3

Adjusted ordinal regression analyses (OR=odds ratio; CI – Confidence Interval) by participant characteristics

Scenario	Model	OR	95% CI	p-value
A different, but related, health condition	Subject Type			
	Control vs Case	1.43	0.94, 2.18	0.10
	Relative vs Case	1.4	0.80, 2.45	0.24
	Gender	1.03	0.68, 1.55	0.89
	Cancer at baseline	**0.61**	**0.41, 0.90**	**0.01**
	Cancer at follow-up	0.77	0.52, 1.15	0.20
	Stage of cancer at follow-up	**3.89**	**1.46, 10.39**	**0.01**
An unrelated health condition or cancer	Subject Type			
	Control vs Case	1.19	0.76, 1.86	0.46
	Relative vs Case	1.48	0.83, 2.63	0.19
	Gender	1.15	0.74, 1.76	0.54
	Cancer at baseline	0.68	0.45, 1.02	0.07
	Cancer at follow-up	0.9	0.60, 1.37	0.63
	Stage of cancer at follow-up	**3.42**	**1.25, 9.32**	**0.02**
New genetic factors	Subject Type			
	Control vs Case	1.34	0.87, 2.06	0.19
	Relative vs Case	1.35	0.76, 2.40	0.31
	Gender	0.99	0.65, 1.51	0.10
	Cancer at baseline	0.68	0.46, 1.01	0.06
	Cancer at follow-up	0.88	0.59, 1.32	0.55
	Stage of cancer at follow-up	**4.39**	**1.59, 12.11**	**0.01**
Share de-identified data	Subject Type			
	Control vs Case	1.14	0.74, 1.78	0.55
	Relative vs Case	0.97	0.53, 1.77	0.91
	Gender	1.14	0.74, 1.75	0.54
	Cancer at baseline	0.85	0.57, 1.28	0.44
	Cancer at follow-up	1.1	0.72, 1.67	0.66
	Stage of cancer at follow-up	**3.49**	**1.30, 9.37**	**0.01**
Minor reaches majority age	Subject Type			
	Control vs Case	1.6	0.93, 2.74	0.09
	Relative vs Case	0.58	0.22, 1.47	0.25
	Gender	**1.71**	**1.01, 2.89**	**0.04**
	Cancer at baseline	0.69	0.41, 1.16	0.16
	Cancer at follow-up	1.03	0.61, 1.75	0.91
	Stage of cancer at follow-up	2.74	0.80, 9.34	0.11

* statistically significant results ($p \leq 0.05$) indicated in **bold**

** Scoring of dependent variables as follows: 1) agree and strongly agree as 1, neutral as 2, disagree and strongly disagree as 3; and, 2) yes, ask permission again as 1, no need to ask, but notify me as 2, and no need to ask or notify as 3